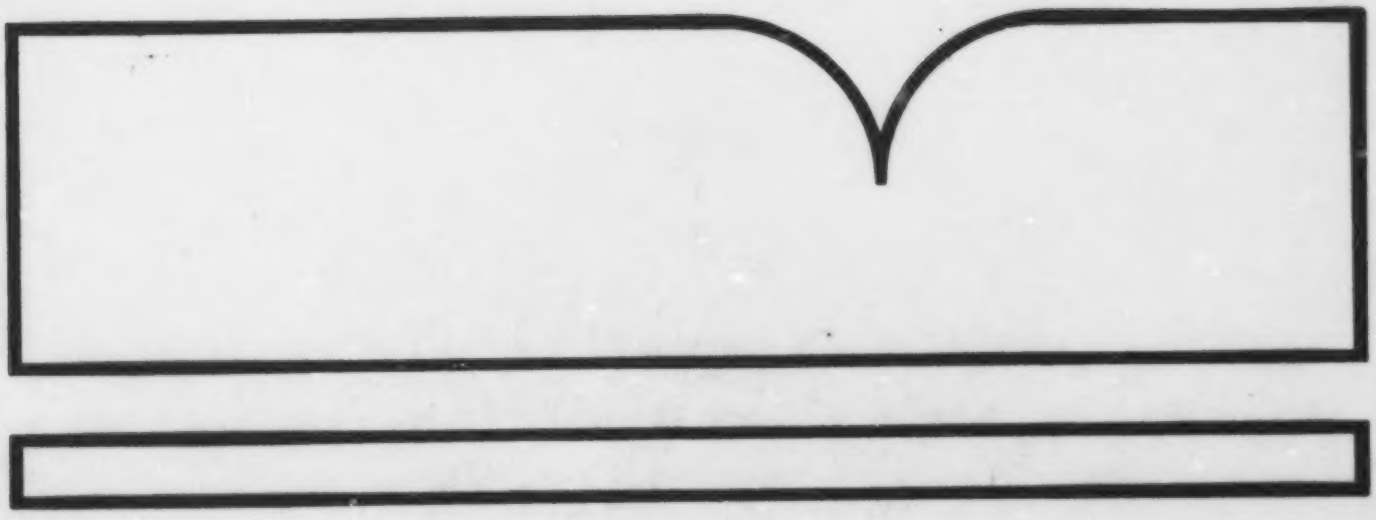
PB82-127432

Dopamine Depletion Slows Retinal Transmission

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

Sep 81



U.S. Department of Commerce
National Technical Information Service
NTIS

PB82-127432

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/J-80-014	2. JOURNAL ARTICLE
3. RECIPIENT'S ACCESSION NO.	
4. TITLE AND SUBTITLE: Dopamine Depletion Slows Retinal Transmission	5. REPORT DATE: September 1981
	6. PERFORMING ORGANIZATION CODE: 308045
7. AUTHOR(S): Robert S. Dyer, William E. Howell, and Robert C. MacPhail	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Neurotoxicology Division, Health Effects Research Lab, US Environmental Protection Agency, Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO.: ACSL1A
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Office of Research and Development (RTP,NC), Health Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE: EPA-600/11

15. SUPPLEMENTARY NOTES

Published In: Experimental Neurology 71: 326-340, 1981

16. ABSTRACT

In male hooded rats, depletion of norepinephrine and dopamine by a-methyl-para-tyrosine (AMT) significantly increased the latencies of early peaks in flash-evoked potentials recorded from the visual cortex, lateral geniculate nucleus, and optic tract. These effects were not produced by depletion of norepinephrine by FLA-63, blockade of muscarinic acetylcholine receptors by scopolamine, or blockade of opiate receptors by naloxone. AMT effects occured only when flashes were used; optic tract stimulation failed to reveal the drug-induced changes. In a dose-response study, haloperidol produced effects similar to those of AMT. L-Dopa + RO4-4602 reversed some of the effects of AMT. It is concluded that depletion of retinal dopamine impairs the timing of retinal responses to light.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

18. DISTRIBUTION STATEMENT: RELEASE TO PUBLIC	19. SECURITY CLASS (This Report): UNCLASSIFIED	21. NO. OF PAGES
	20. SECURITY CLASS (This page): UNCLASSIFIED	22. PRICE

EXPERIMENTAL NEUROLOGY 71, 326–340 (1981)

EPA-600/J-80-014
Journal Article

Dopamine Depletion Slows Retinal Transmission

ROBERT S. DYER, WILLIAM E. HOWELL, AND ROBERT C. MACPHAIL[1]

Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Received May 19, 1980; Revision received July 31, 1980

In male hooded rats, depletion of norepinephrine and dopamine by α-methyl-*para*-tyrosine (AMT) significantly increased the latencies of early peaks in flash-evoked potentials recorded from the visual cortex, lateral geniculate nucleus, and optic tract. These effects were not produced by depletion of norepinephrine by FLA-63, blockade of muscarinic acetylcholine receptors by scopolamine, or blockade of opiate receptors by naloxone. AMT effects occurred only when flashes were used; optic tract stimulation failed to reveal the drug-induced changes. In a dose–response study, haloperidol produced effects similar to those of AMT. L-Dopa + RO4-4602 reversed some of the effects of AMT. It is concluded that depletion of retinal dopamine impairs the timing of retinal responses to light.

INTRODUCTION

Dopamine-containing neurons are known to occur in the retina (11) but their functional significance remains unclear. Photic stimulation increases release of dopamine (14) and stimulates tyrosine hydroxylase activity (13) in the retina. In most mammals the dopamine-containing cells appear to be a subpopulation of amacrine cells, having cell bodies in the inner nuclear layer and processes in the inner plexiform layer (9). In spite of their relatively accessible location, surprisingly little work has explored their functional properties in mammals. A recent report from the clinical literature provides some data which may bear directly on the role of dopamine in visual function. Bodis-Wollner and Yahr (2) demonstrated

Abbreviations: VEP—visual evoked potential, AMT—α-methyl-*para*-tyrosine.

[1] The authors wish to thank Mark Bercegeay and Leon Lamm for assistance with surgery and data collection, Larry Cook for the catecholamine assays, the Health Effects Research Laboratory Word Processing Center for preparation of the manuscript, Phyllis Keeter for secretarial assistance, and Vernon Benignus, Ivan Bodis-Wollner, Jacques Maurissen, William Merigan, and David Otto for helpful comments.

0014-4886/81/020326-15$02.00/0

Copyright © 1981 by Academic Press, Inc.
All rights of reproduction in any form reserved.

that patients suffering from Parkinson's disease had significantly longer visual evoked potential (VEP) peak latencies than age-matched controls. A reasonable inference from their work might be that the disease slowed conduction velocity. The finding that L-Dopa therapy partially reversed the changes suggested that dopamine depletion may have caused them. Although diagnostic VEP testing has become common among certain populations of patients (15), the technique will be more useful when the significance of observed alterations is understood. Thus, in understanding the alterations in patients with Parkinson's disease, it is important to know whether the effects are truly due to altered conduction velocities, or to altered retinal, thalamic, or cortical function.

The VEP has also become a popular test in assessing potentially neurotoxic substances (7). For reasons similar to those mentioned above, it is important to know the functional significance of alterations observed to follow exposure to chemical agents. We report here that dopamine depletion, but not norepinephrine depletion, selectively increased the latencies of early peaks in the VEP recorded from the rat cortex, lateral geniculate nucleus, and optic tract, and furthermore decreased the amplitude of certain peaks. Blockade of dopamine receptors produced similar results. Our studies indicate that this effect occurred in the retina, because optic tract stimulation failed to produce equivalent alterations.

METHODS

Seventy-six male hooded rats were obtained from Charles River Breeding Company, and at 60 days of age were implanted with electrodes for recording the VEP. A 00-90 stainless-steel screw placed 5.5 mm posterior to bregma and 3.0 mm lateral to the midline served as the visual cortex recording electrode, and 0-80 screws placed 1 mm anterior and 1 mm left and right of bregma served as reference and ground, respectively. Five rats also had a bipolar electrode placed in the optic tract (0.2 mm posterior to bregma, 2.0 mm lateral), and a lateral geniculate electrode (3.2 mm posterior to bregma, 3.2 mm lateral) ipsilateral to the visual cortex electrode. Flash-evoked potentials were recorded during placement of the depth electrodes. Each of the two depth electrodes was cemented in place when the recorded amplitude reached a maximum. Details of the surgical and recording procedures may be obtained elsewhere (7). Briefly, after 2 weeks of recovery, the animals were treated with the appropriate drug, had the pupils dilated with one drop per eye of 1% cyclopentolate hydrochloride (Cyclogyl), and were placed in a recording chamber with mirrors on three walls and a strobe outside the fourth. The Grass PS22 strobe was flashed at its highest intensity, producing a flash 10 μs in

duration. Peak power, measured in the center of the recording chamber, was 4.53×10^7 lux. This high intensity was used to provide supramaximal stimulation of the retina, thereby minimizing potential variations in retinal illumination resulting from altered body orientation.

In all experiments except the second, an average of 64 flashes presented at 0.5 Hz was obtained using conventional amplifiers (low- and high-frequency cutoffs set at 1.0 Hz and 10 kHz, respectively) and summed by a Nicolet 1024 signal averager with 0.4 ms/data point resolution. Amplitudes and latencies of the first three positive and negative waves were obtained according to previously determined conventions (10) and the waveforms displayed on a Hewlett–Packard X–Y plotter. The data from all experiments reported here were subjected first to a randomized block multivariate analysis of variance, with animals as blocks. Upon finding significant overall effects of the drugs upon the 11 variables measured (P1, N1, P2, N2, P3, and N3 latencies; P1N1, N1P2, P2N2, N2P3, and P3N3 amplitudes), a separate analysis of variance was used to evaluate each variable, with $\alpha = 0.005$ to test the hypothesis of no difference between the saline and drug means. This level of significance was used to keep the probability of at least one Type I error for the 11 tests at about 0.05 for each variable.

In the first experiment, 20 animals with cortical electrodes were subjected once to each of five drug conditions. These drug treatments occurred once every 3 days and were counterbalanced to prevent order-of-testing effects. The drugs and respective treatment times were: (a) scopolamine, 2 mg/kg 15 min prior to testing; (b) naloxone, 1 mg/kg 15 min prior to testing; (c) FLA-63, a dopamine-β-hydroxylase inhibitor, 25 mg/kg 4 h prior to testing; (d) α-methyl-*para*-tyrosine (AMT), 75 mg/kg 6 h and 75 mg/kg 2 h prior to testing; and (e) normal saline, 2 ml/kg 6 h and 2 ml/kg 15 min prior to testing, to control for the extremes of the dosing regimens prescribed for the other substances.

In the second experiment, only saline, FLA-63, and AMT were given, and only the animals with depth electrodes were used. The dosing regimen was the same in both experiments, and again order of presentation was counterbalanced. The procedure for the second experiment had five parts. First, the animals received four consecutive trials of 32×1-Hz optic tract stimulation with recordings taken from the cortex. The stimuli were biphasic constant-current square waves, 0.1 ms per phase. The stimulation intensities, which were determined before the experiment began, remained constant for a particular animal and averaged 0.33 mA. Each animal's stimulus intensity was chosen to clearly differentiate the peaks of the evoked potential. Part 2 consisted of four consecutive trials of 32×1-Hz optic tract stimulation with recordings taken from the lateral geniculate

nucleus. The third, fourth, and fifth parts each involved four trials of 64 × 1-Hz flashes, with recordings taken from the cortex, lateral geniculate nucleus, and optic tract, respectively.

In the third experiment, 18 animals were injected 90 min prior to testing with either 0.00 (saline vehicle), 0.05, 0.15, or 0.30 mg/kg α-flupenthixol, a dopamine receptor blocker. Each animal received each dose, and order of presentation was counterbalanced across animals. Time between doses was 72 h.

In the fourth experiment, 22 animals were injected 60 min prior to testing with either 0.00 (0.1% tartaric acid vehicle), 0.125, 0.250, or 0.500 mg/kg haloperidol, another dopamine receptor blocker. Each animal received each dose, and order of presentation was counterbalanced across animals. Time between doses was 72 h.

In the fifth experiment, 11 animals were injected with either: (a) AMT (75 mg/kg 6 h and 75 mg/kg 2 h prior to testing) + saline (the RO4-4602 vehicle, 90 min prior to testing) + 0.1% w/v tartaric acid (the L-Dopa vehicle, 60 min prior to testing); (b) AMT (75 mg/kg 6 h and 75 mg/kg 2 h prior to testing) + RO4-4602 (50 mg/kg, 90 min prior to testing) + L-Dopa (100 mg/kg 60 min prior to testing; or (d) saline (2 ml/kg 6 h, 2 ml/kg 2 h, and 1 ml/kg 90 min prior to testing) + 0.1% tartaric acid (10 ml/kg, 60 min prior to testing). These four groups were designated A+V+V, A+R+L, V+R+L, and V+V+V, respectively. All animals received each of the four treatments in counterbalanced order. Time between treatments was 1 week.

Drug Preparation and Treatment. The tyrosine hydroxylase inhibitor, α-methyl-*para*-tyrosine methyl ester HCl, was obtained from Sigma Chemicals (St. Louis, Missouri) and was dissolved in normal saline and administered in a volume of 2 ml/kg body weight. The dose was 75 mg base/kg body weight given 6 h prior to testing and again 2 h prior to testing, a total dosage of 150 mg. FLA-63 (bis(4-methyl-1-homopiperazinylthiocarbonyl)-disulfide), an inhibitor of dopamine-β-hydroxylase, was obtained from Regis Chemicals (Chicago, Illinois). The drug was prepared by dissolving it in warm saline with a few drops of 1 N HCl added and then adjusting the *p*H to neutrality with 1 N NaOH. FLA-63 was injected in a dose of 25 mg/kg body weight, 4 h prior to testing and in a volume of 4 ml/kg body weight. L-Dopa (*l*-(3,4-dihydroxyphenylalanine) was obtained from Regis Chemicals and was dissolved in 0.1% warm tartaric acid. The drug was administered at a dose of 100 mg/kg body weight 60 min prior to testing, and in a volume of 10 ml/kg body weight. The rats also received 50 mg/kg RO4-4602, an inhibitor of the enzyme *l*-aromatic amino acid decarboxylase, 30 min prior to L-Dopa, in a volume of 1 ml/kg. RO4-4602 was supplied by Hoffmann-La Roche, Inc. (Nutley, New Jersey) and was dissolved in normal saline.

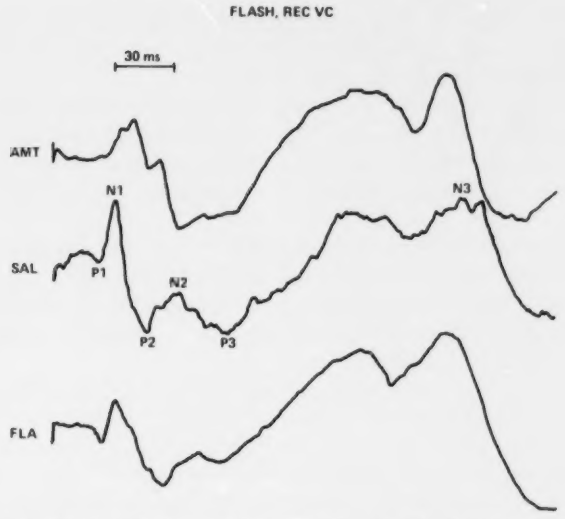


FIG. 1. Averaged flash-evoked potentials recorded from the visual cortex of a single rat after treatment with saline (SAL), α-methyl-*para*-tyrosine (AMT), or FLA-63 (FLA). There are 64 trials per average. The flash occurred at the vertical inflection beginning each tracing, and the epoch duration was 409.6 ms. Note the increased N1 latency after AMT treatment.

Haloperidol, a dopamine antagonist, was supplied by McNeil Laboratories (Fort Washington, Pennsylvania), and was dissolved in 0.1% tartaric acid. The drug was injected 60 min prior to testing in doses of 0.125 to 0.5 mg/kg body weight and in a volume of 1 ml/kg body weight. The muscarinic cholinergic antagonist, scopolamine HBr, was obtained from Sigma Chemicals and was dissolved in normal saline and administered 30 min prior to testing at a dose of 2 mg base/kg body weight, in a volume of 1 ml/kg body weight. The narcotic antagonist, naloxone HCl, was obtained from Endo Laboratories (Garden City, New Jersey). It was dissolved in normal saline and administered at 1 mg salt/kg body weight 15 min prior to testing in a volume of 1 ml/kg body weight. All drugs were administered i.p.

RESULTS

Some of the drugs administered during these studies have behavioral effects, which may have influenced the data. Although no systematic attempts were made to assess behavior, random checks during recording sessions indicated that animals were awake and had their eyes open.

In the first experiment, only AMT produced alterations in evoked potential latencies. Figure 1 shows the effects of saline, AMT, and FLA-63

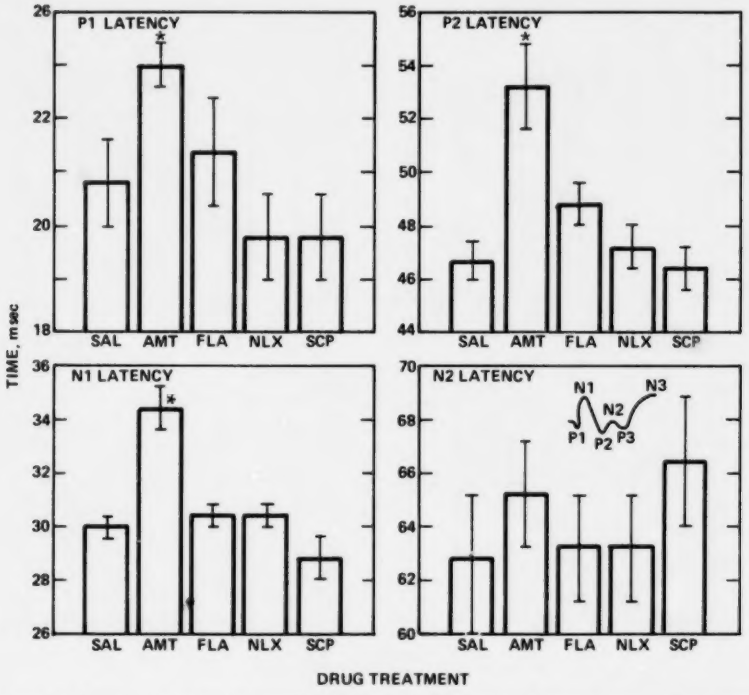


FIG. 2. Mean peak latencies recorded from animals under each drug treatment during the first experiment. In this and all other figures, vertical bars represent ±1 SE of the mean. Sal—saline, AMT—α-methyl-*para*-tyrosine, FLA—FLA-63, NLX—naloxone, and SCP—scopolamine. *—Different from saline control, $P < 0.005$.

upon the evoked potentials of one rat representative of the group. The average peak latencies for the different groups are illustrated in Fig. 2. AMT significantly increased the latency of early peaks (P1, N1, and P2), but did not significantly alter latencies of later peaks (N2, P3, and N3).

The effects of the different drug treatments upon evoked potential amplitudes are shown in Fig. 3. There were no significant drug-induced alterations in P1N1 amplitudes. AMT significantly reduced N1P2 and P2N2 amplitudes. N2P3 and P3N3 amplitudes were not significantly altered by the drug treatments.

Although P1, N1, and P2 latencies were all increased by AMT, visual inspection of the data suggested that the waveform was not equally shifted at all peaks. If the whole waveform were shifted, then the difference between P1 and P2 latencies should have remained constant. Analyses of

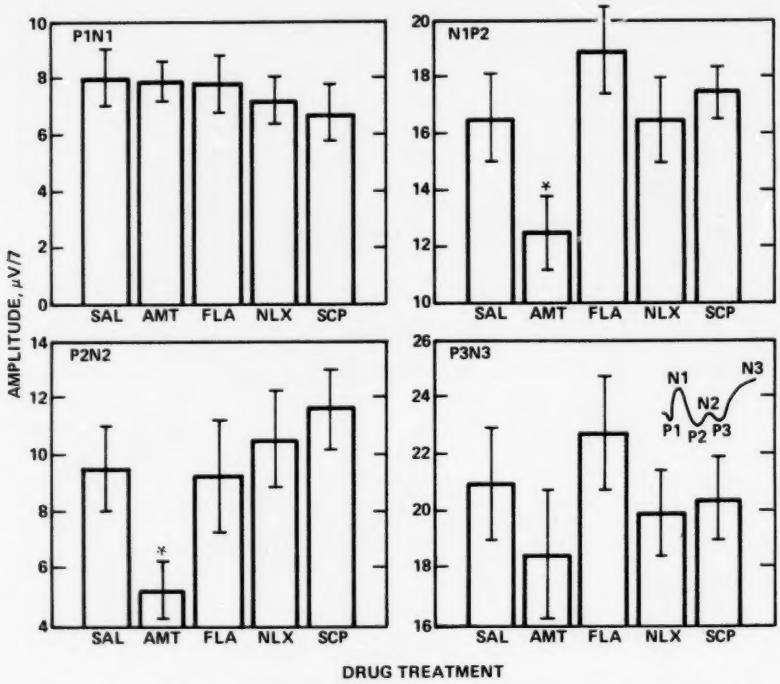


FIG. 3. Mean peak-to-peak amplitudes recorded from animals under each drug treatment during the first experiment. To convert ordinate to μV, multiply by 7. *—Different from control, $P < 0.005$.

variance on the N1-P1 latency differences, the P2-P1 latency differences, and the P2-N1 latency differences showed that the shift was uneven. The P2-P1 latency difference was not constant across drug treatments. Rather, in the case of AMT the mean time (±SE) between the two peaks (29.3 ± 1.55 ms) was significantly longer than for the saline treatment (24.9 ± 1.14 ms). Similarly, the time from P1 to N1 was longer after AMT (10.4 ± 0.80 ms) than after saline treatment (8.2 ± 0.80 ms). The P2-N1 latency differences were not significantly altered by the drug treatments.

The second experiment replicated the latency alterations produced by AMT in the flash-evoked potential recorded from the cortex that were obtained in the first experiment. Electrical stimulation of the optic tract, however, did not reveal drug-induced alterations in peak latencies or amplitudes. Figure 4 illustrates the failure to find any AMT-induced alteration in the latencies recorded from the cortex after optic tract

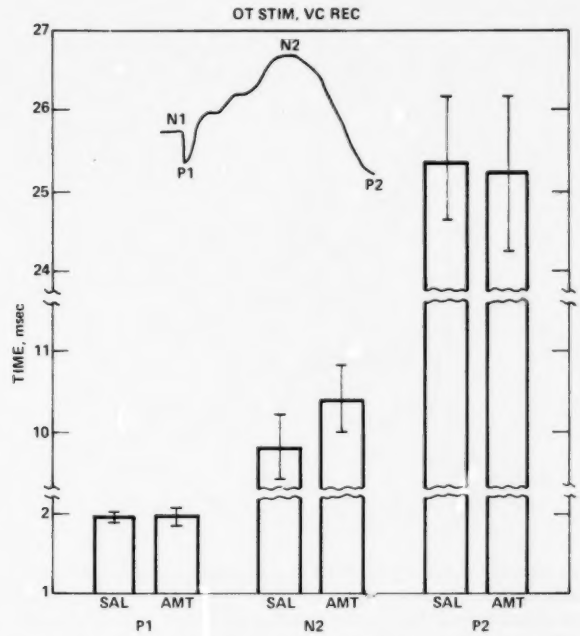


FIG. 4. Mean latencies recorded from the visual cortex after optic tract stimulation in animals treated with AMT or saline. Peak designations are indicated on the diagram of a typical waveform. These results illustrate that when stimulation of the retina was bypassed, the effects of AMT were not present.

stimulation. On the other hand, flash-evoked potentials recorded from the optic tract and lateral geniculate nucleus revealed alterations similar to those found in the cortex. Figure 5 illustrates the influence of AMT upon the response recorded from the optic tract of one animal. In this animal, the light was flashed at 2 Hz, and 10 averages of 128 flashes each were recorded. The latency of the first negative peak was 22.6 ± 0.3 ms before AMT, and 24.4 ± 0.4 ms after.

Approximate dopamine depletion was assessed in a separate series of rats injected with either saline ($N = 6$) or AMT ($N = 6$) according to the same schedule as above. Radioenzymatic assay of the retinas according to the method of Coyle and Henry (5) indicated that dopamine in the AMT-treated retinas was depleted by greater than 50% (controls: 208.7 ng/g; AMT: 101.3 ng/g).

In the third experiment, overall multivariate analysis of variance indicated that the effect of α-flupenthixol was not significant. The fourth

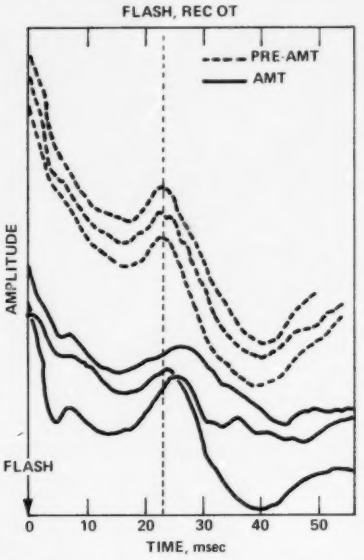


FIG. 5. Three consecutive averages of flash-evoked potentials recorded from the optic tract of one rat before and after treatment with AMT. Each average is the mean of 128 flashes. The vertical line illustrates that all AMT peaks occurred later than predrug controls. The figure demonstrates that the effects of AMT were demonstrable before any postretinal synapses.

experiment revealed that haloperidol did produce significant alterations in the VEP. The latter results are summarized in Figs. 6 and 7. Figure 6 indicates the significant increase in P1 and N1 latencies produced by haloperidol; P2 latencies increased slightly, but not significantly ($P < 0.036$). Figure 7 illustrates the significant increase in P3N3 amplitude produced by haloperidol.

Results of the fifth experiment are shown in Figs. 8 and 9. As in the first experiment, AMT increased latencies of P1, N1, and P2 peaks relative to the V+V+V control. RO4-4602 + L-Dopa increased P1 and N1 latencies, but not P2 latencies. AMT + RO4-4602 + L-Dopa also increased P1 and N1 latencies, but not P2 latencies. AMT in this experiment did not significantly alter any amplitudes. AMT + RO4-4602 + L-Dopa depressed the amplitudes of P1N1, N1P2, and P3N3 relative to the V+V+V control. RO4-4602 + L-Dopa produced mean values almost identical to those of AMT + RO4-4602 + L-Dopa, but only the P3N3 depression was statistically significant. As in the first experiment, AMT increased the duration of the P1N1P2 complex (P2-P1 latency difference) relative to control. None of the other treatments significantly altered this parameter.

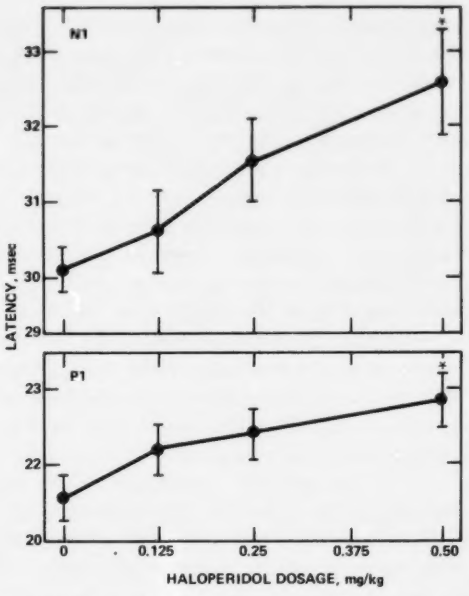


FIG. 6. Mean P1 and N1 flash-evoked peak latencies recorded from the visual cortex of rats after haloperidol treatment. The figure illustrates that blockade of dopamine receptors was as effective as dopamine depletion in increasing these latencies. *—Different from control, $P < 0.005$.

DISCUSSION

The results indicate that AMT increased early latencies, and in experiment 1, depressed amplitudes of two early peaks (N1P2 and P2N2) in the flash-evoked potential from the visual cortex in the hooded rat. Because these effects were not produced by FLA-63, it seems likely that they resulted from dopamine depletion. Failure to find latency alterations in cortical recordings when the optic tract was electrically stimulated supports the argument that the origin of the alterations was in the retina. Electrical stimulation is obviously not equivalent to photic stimulation. However, for the purpose of this demonstration, the differences do not alter interpretation. The drug-induced alterations in latency can originate either in the retina, in the optic tract, between the tract and the cortex, or in the cortex. If the alterations occurred central to the tract electrode, then they should not be present in flash-evoked recordings obtained from the tract. However, the second experiment demonstrated alterations at the optic tract level. Thus, the origins must be either in the retina or in the tract.

If the drug-induced alterations were manifestations of a slowed conduction velocity, then it is likely that stimulation of the tract would reveal latency differences recorded at the cortex. No such differences were found. Although there is evidence that dopamine content in the cortex may be altered by sensory stimulation (16), the concentration of dopamine in the retina (11) and its alteration by photic stimulation (14) support the contention that the locus of the present effect is retinal.

The failure of α-flupenthixol to increase early peak latencies, contrasted with the haloperidol-induced latency increases, deserves comment. In an investigation of ^{14}C-labeled dopamine disappearance in mouse brain, Hyttel (12) demonstrated that the maximally effective dose of α-flupenthixol was 0.31 mg/kg. This dosage enhanced the disappearance of labeled dopamine by 51%. Approximately the same magnitude of effect was obtained with a dose of haloperidol between 0.08 and 0.16 mg/kg. Haloperidol was also maximally effective at 0.31 mg/kg, with approximately 71% disappearance of labeled dopamine. Thus, the highest dose of α-flupenthixol used in the present experiment (0.30 mg/kg) might be expected to produce about the same effect as the lowest dose of haloperidol used (0.125 mg/kg). In fact, when latencies of P2 under drug conditions are expressed as a percentage of the zero-dosage values from the same

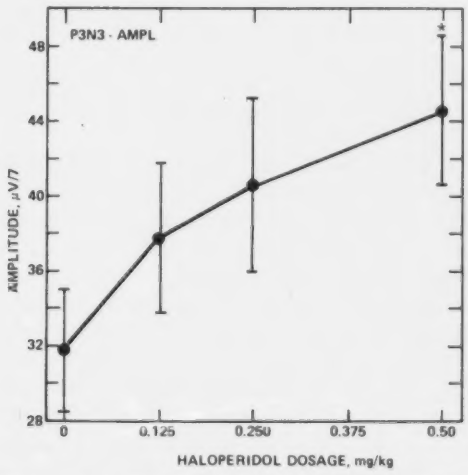


FIG. 7. Mean flash-evoked P3N3 amplitudes recorded from the visual cortex after haloperidol treatment. The figure illustrates that there were effects of dopamine blockade upon flash-evoked potentials which are not easily attributed to retinal dysfunction. To convert ordinate to μV, multiply by 7. *—Different from control, $P < 0.005$.

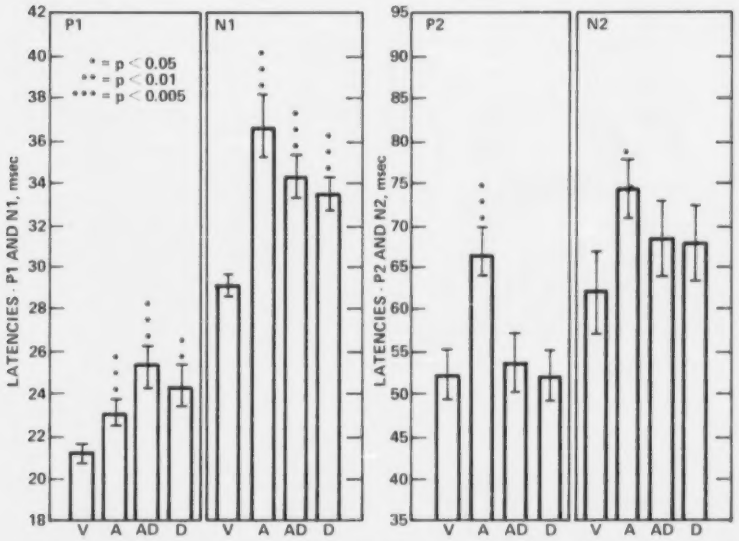


FIG. 8. Mean peak latencies of flash-evoked potentials recorded from the visual cortex of animals after treatment with V (vehicle + vehicle + vehicle), A (AMT + vehicle + vehicle), AD (AMT + RO4-4602 + L-Dopa), or D (vehicle + RO4-4602 + L-Dopa). The figure illustrates that RO4-4602 and L-Dopa treatment prevented the effects of AMT on P2 latencies, but not P1 or N1 latencies. Paradoxically, RO4-4602 + L-Dopa produced AMT-like effects upon P1 and N1 latencies when given alone.

experiment, it is clear that 0.125 mg/kg haloperidol did produce almost exactly the same (nonsignificant) latency changes as 0.30 mg/kg α-flupenthixol (107 vs. 108%). Haloperidol administration produces drowsiness (4), which might be manifested by eye closure and consequent decreased retinal stimulation. It is unlikely that eye closure produced the effects reported here. Reducing retinal stimulation has been shown to reduce P1N1, N1P2, and P3N3 amplitudes in hooded rats (8). In the present study, P1N1 and N1P2 amplitudes were not altered by haloperidol exposure, and P3N3 amplitudes were increased. Decreased P3N3 amplitudes have been associated with pharmacologically induced arousal (10), and therefore haloperidol-induced drowsiness may account for the dose-related increase in P3N3 amplitudes recorded here.

The data from the RO4-4602 + L-Dopa experiment do not lend themselves to a simple interpretation. The failure to replicate the AMT-induced decrement in N1P2 amplitude observed during the first experiment may have resulted from using roughly half the number of

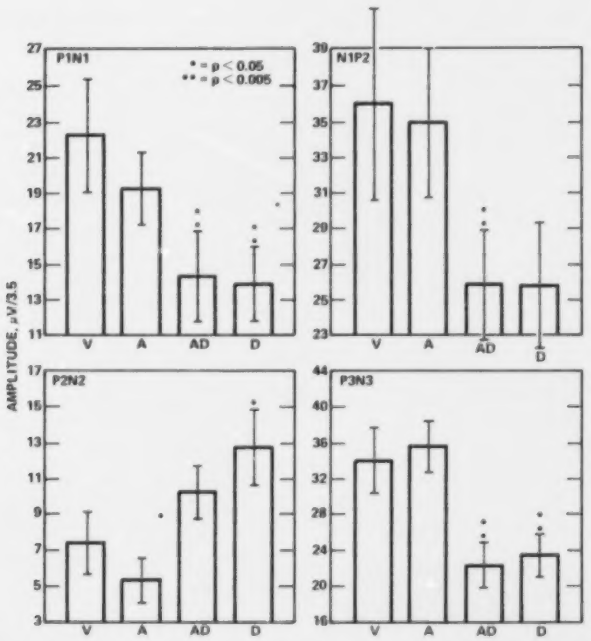


FIG. 9. Mean peak-to-peak amplitudes of flash-evoked potentials recorded from the visual cortex after treatments V (vehicle + vehicle + vehicle), A (AMT + vehicle + vehicle), AD (AMT + RO4-4602 + L-Dopa), or D (vehicle + RO4-4602 + L-Dopa). To convert ordinate to μV, multiply by 3.5.

subjects in the RO4-4602 + L-Dopa experiment. The influence of these compounds upon P2 latency was as predicted: they prevented the increased latency otherwise produced by AMT. Contrary to expectation, the combination of these drugs failed to prevent AMT-induced increases in P1 and N1 latencies. Indeed, the RO4-4602 + L-Dopa treatment alone produced some of the latency alterations expected from AMT (increased P1 and N1 latencies). This may indicate that RO4-4602 is not totally excluded by the blood–retina barrier.

Straschill and Perwein (18) showed that cats given intravenous L-Dopa had longer latency and lower amplitude flash-evoked potentials in the optic tract than controls. Since the wave duration was not increased, they argued that L-Dopa had not desynchronized ganglion cell responses, but had merely reduced them. The same study demonstrated that iontophoretic application of dopamine reduced both spontaneous and light-evoked

activity in 90% of ganglion cells tested. These results parallel the present findings with RO4-4602 + L-Dopa, in which there was an increased latency, decreased P1N1 amplitude, but no increased P1-to-P2 time. Thus, both adding and subtracting dopamine to the retinal system alters timing of retinal responses to light. Dopamine depletion appears to desynchronize responses to light flash (increases wave latency and durations) and may increase the actual number or frequency of ganglion cell responses (maintained P1N1 amplitude in the face of increased P1-P2 duration). Verification of this hypothesis awaits analysis of ganglion cell responses in dopamine-depleted animals.

Retinal dopamine-containing neurons are usually considered to be a type of amacrine cell (3, 9). If it is at the amacrine cell level that dopamine depletion produces the alterations in latency and amplitude of the cortical evoked potential, it is possible to postulate the mechanisms by which such alterations may be effected. Werblin (19) suggested that in the mudpuppy, amacrine cells play a role in the rapid and synchronous conversion of graded potentials from the more exterior retinal layers into action potentials at the ganglion cells. It thus follows that partial impairment of amacrine cell function, as would be expected by dopamine depletion, should provide a desynchronizing influence on ganglion cell responsiveness.

These findings have several implications for patients with known dopamine depletion. First, it seems reasonable to assume that in the case of Parkinson's disease, the delay in evoked potentials recorded from the scalp (2) is produced at the retina, as it was by dopamine depletion in the rats of this study. Second, if dopamine depletion alters the timing of ganglion cell responses, it would not be surprising to find that patients with Parkinson's disease have an altered ability to resolve rapidly flickering light.

Visual evoked potentials are diagnostically useful for a number of neurological conditions (1). The data presented here indicate that alterations in retinal function produced by dopamine depletion may be detected using the VEP technique. In view of these findings, it may be that some of the reported VEP differences between schizophrenic and control subjects (17) are related to phenothiazine-induced alterations in dopaminergic systems.

REFERENCES

1. BECK, E. C., R. E. DUSTMAN, AND E. G. LEWIS. 1975. The use of the average evoked potential in the evaluation of central nervous system disorders. *Int. J. Neurol.* **9**: 211–232.
2. BODIS-WOLLNER, I., AND M. D. YAHR. 1978. Measurements of visual evoked potentials in Parkinson's disease. *Brain* **101**: 661–671.
3. BOYCOTT, B. B., J. E. DOWLING, S. K. FISHER, H. KOLB, AND A. M. LATIES. 1975.

Interplexiform cells of the mammalian retina and their comparison with catecholamine-containing retinal cells. *Proc. R. Soc. B.* **191:** 353–368.

4. BYCK, R. 1975. Drugs used in the treatment of psychoses. Pages 152–200 in L. S. GOODMAN, AND A. GILMAN, Eds., *The Pharmacological Basis of Therapeutics*. 5th ed. Macmillan, New York.
5. COYLE, J. T., AND D. HENRY. 1973. Catecholamines in fetal and newborn rat brain. *J. Neurochem.* **21:** 61–67.
6. DYER, R. S., AND Z. ANNAU. 1977. Flash evoked potentials from rat superior colliculus. *Pharmacol. Biochem. Behav.* **6:** 453–459.
7. DYER, R. S., C. U. ECCLES, AND Z. ANNAU. 1978. Evoked potential alterations following prenatal methylmercury. *Pharmacol. Biochem. Behav.* **8:** 137–141.
8. DYER, R. S., AND H. S. SWARTZWELDER. 1978. Sex and strain differences in the visual evoked potentials of albino and hooded rats. *Pharmacol. Biochem. Behav.* **9:** 301–306.
9. EHINGER, B. 1976. Biogenic amines as transmitters in the retina. Pages 145–163. in S. L. BOTING, Ed., *Transmitters in the Visual Process*. Pergamon, Oxford.
10. FLEMING, D. E., D. E. SHEARER, AND J. J. CREEL. 1974. Effect of pharmacologically induced arousal on the evoked potential in the unanesthetized rat. *Pharmacol. Biochem. Behav.* **2:** 187–192.
11. HAGGENDAL, J., AND T. MALMFORS. 1965. Identification and cellular localization of the catecholamines in the retina and choroid of the rabbit. *Acta Physiol. Scand.* **54:** 58–66.
12. HYTTEL, J. 1974. Effect of neuroleptics on the disappearance rate of ^{14}C labeled catecholamines formed from ^{14}C tyrosine in mouse brain. *J. Pharm. Pharmacol.* **26:** 588–596.
13. IUVONE, P. M., C. L. GALLI, C. K. GARRISON-GUND, AND N. H. NEFF. 1978. Light stimulates tyrosine hydroxylase activity and dopamine synthesis in retinal amacrine neurons. *Science* **202:** 901–902.
14. KRAMER, S. G. 1971. Dopamine: a retinal neurotransmitter. I. Regional uptake, storage and light stimulated release of H3-dopamine *in vivo*. *Invest. Opthalmol.* **10:** 438–452.
15. NEETENS, A., Y. HENDRATA, AND J. VAN ROMPAEY. 1979. Pattern and flash visual evoked responses in multiple sclerosis. *J. Neurol.* **220:** 113–124.
16. READER, T. A., J. DECHAMPLAIN, AND H. JASPER. 1976. Catecholamines released from cerebral cortex in the cat: decrease during sensory stimulation. *Brain Res.* **111:** 95–108.
17. SHAGASS, C. 1972. *Evoked Brain Potentials in Psychiatry*. Plenum, New York.
18. STRASCHILL, M., AND J. PERWEIN. 1974. The inhibition of retinal ganglion cells by catecholamines and γ-aminobutyric acid. *Pflügers Arch.* **312:** 45–54.
19. WERBLIN, F. S. 1977. Regenerative amacrine cell depolarization and formation of on–off ganglion cell response. *J. Physiol. (London)* **264:** 767–785.